A DISSERTATION ON

CLINICAL FEATURES DIRECTED SCREENING FOR HIV INFECTION AMONG CHILDREN ATTENDING AN URBAN REFERRAL CENTRE

M.D (BRANCH VII)

PAEDIATRIC MEDICINE

THE TAMIL NADU
DR.MGR. MEDICAL UNIVERSITY.

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INSTITUTE OF CHILD HEALTH AND HOSPITAL FOR CHILDREN,
MADRAS MEDICAL COLLEGE, CHENNAI.

CERTIFICATE

This is to certify that the dissertation titled, "**Clinical Features Directed Screening For HIV Infection Among Children Attending An Urban Referral Centre"** submitted by **Dr. N.Ramesh**, 2008-2009 session to the Faculty of Pediatrics, The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirements for the award of M.D.Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I, **Dr. N.Ramesh**, solemnly declare that the dissertation titled **"Clinical features directed screening for HIV infection among children attending an urban referral centre"** has been prepared by me.

This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Examination in Pediatrics.

Dr.N.RAMESH

Place: Chennai

Date :

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CERTIFICATE OF APPROVAL

To
Dr. N. Ramesh
PG in MD Paediatrics
Madras Medical College, Chennai -3

Dear Dr. N. Ramesh

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "clinical features directed screening for HIV infected among children attending an urban referral centre" No.19062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. K. Ramadevi MD Prof of Biochemistry, MMC, Ch-3	-- Member
3.	Prof. R. Nandhini MD Director, Inst. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

ACKNOWLEDGEMENT

My sincere thanks to **Prof. Dr.V.Kanagasabai, M.D.,** Dean, Madras Medical College, Chennai for permitting me to utilize the clinical materials of the hospital for the successful execution of my study.

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I sincerely thank all the children and their parents who have submitted themselves for this study.

CONTENTS

INTRODUCTION

EPIDEMIOLIOGY

- 38.6 million - HIV infection world over, 2.3 million, i.e. 5.9 % - children <15 years of age
- In 2007- 5,40,000 children were born with HIV infection transmitted from their infected mothers
- 90% - sub-saharan Africa & remaining in Asia , mainly in India
- Estimated total no. of HIV infection in India :
    - 3.97 million – 2001
    - 5.1 million – 2003
    - 5.134 million – 2004
    - 6.13 million - 2010
- No. Of children living with HIV in India – 0.17 million (UNAIDS report 2004) to 0.24 million(NACO estimate).
- India – 3 zones
- High prevalence - HIV prevalence in ANC mothers > 1%
- Medium prevalence - < 1% but in high risk population in STI clinics >20%
- Low prevalence - <1% & in high risk < 20%

- High prevalence – (6) Maharashtra, Karnataka, Tamil Nadu, Andhra Pradesh, Manipur, Nagaland
- Medium prevalence – (2) Gujarat, West Bengal
- Low prevalence – rest of states
- National average of HIV prevalence in Antenatal mothers – 0.7%
- Mother to child transmission- 15 to 30%- non-breastfeeding population, 30 to 45% - breastfeeding population.

HIV VIRUS

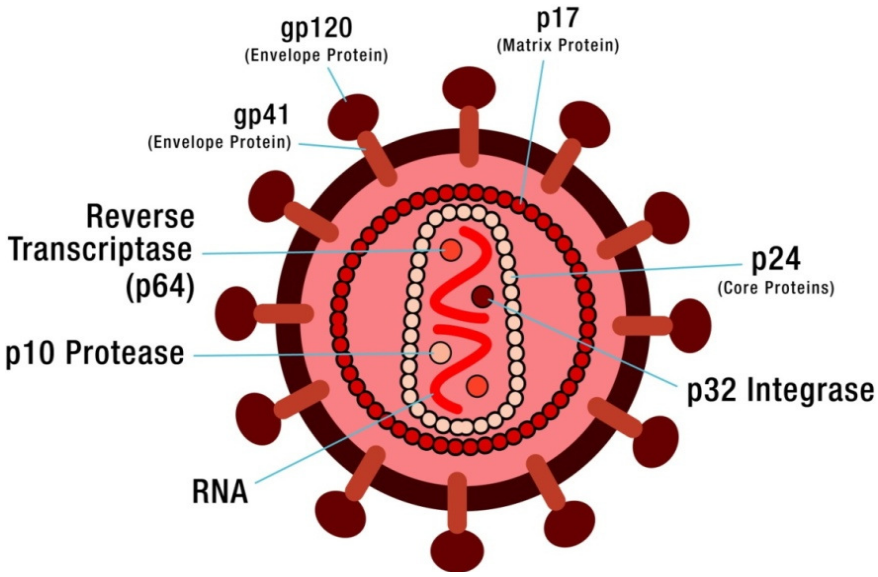
- Robert Galo. 1983.
- RNA Virus
- Retroviridiae, Lentivirus.
- HIV-1,HIV-2
- Three major groups - M,N,O
- M (Major) – 9, subtypes – A,B,C,D,F,G,H,J,K
- Subtype c (common).

MORPHOLOGY

- GAG, POL, ENV
- ENV-gp120, gp41.
- POL-viral enzymes
- GAG- P24, P17, P9, P6.

HIV Virus

Structure



HIV 1

1. TAT, REV, NEF, VIF, VPR, VPU.
2. Does not contain VPX.
3. Commonest in India.

HIV 2

1. Rare in India
2. Common in African countries.
3. Fewer immunological disturbances
4. Low transmissibility
5. Longer incubation period, Low efficiency CD4 binding.

ROUTE OF TRANSMISSION

- Mother to child transmission
- Blood and blood products
- Intravenous Drug users
- Sexual transmission

MOTHER TO CHILD TRANSMISSION

- Commonest
- Perinatal period is most vulnerable.
- Factors influencing transmission

    1. High maternal viraemia
    2. Prolonged rupture of membranes
    3. STDs during pregnancy.

4. Preterm delivery.
5. Obstetric procedures (episeotomy, aminocentesis).
6. Vitamin A deficiency.

RATE OF MOTHER TO CHILD TRANSMISSION

Viral load	**Transmission rate**
<1000 cop/ml	0%
1000-10000	16.6%
10001-50000	21.3%
50001-10000	30.9%
>100000	40.6%

CD4+ MOLECULE

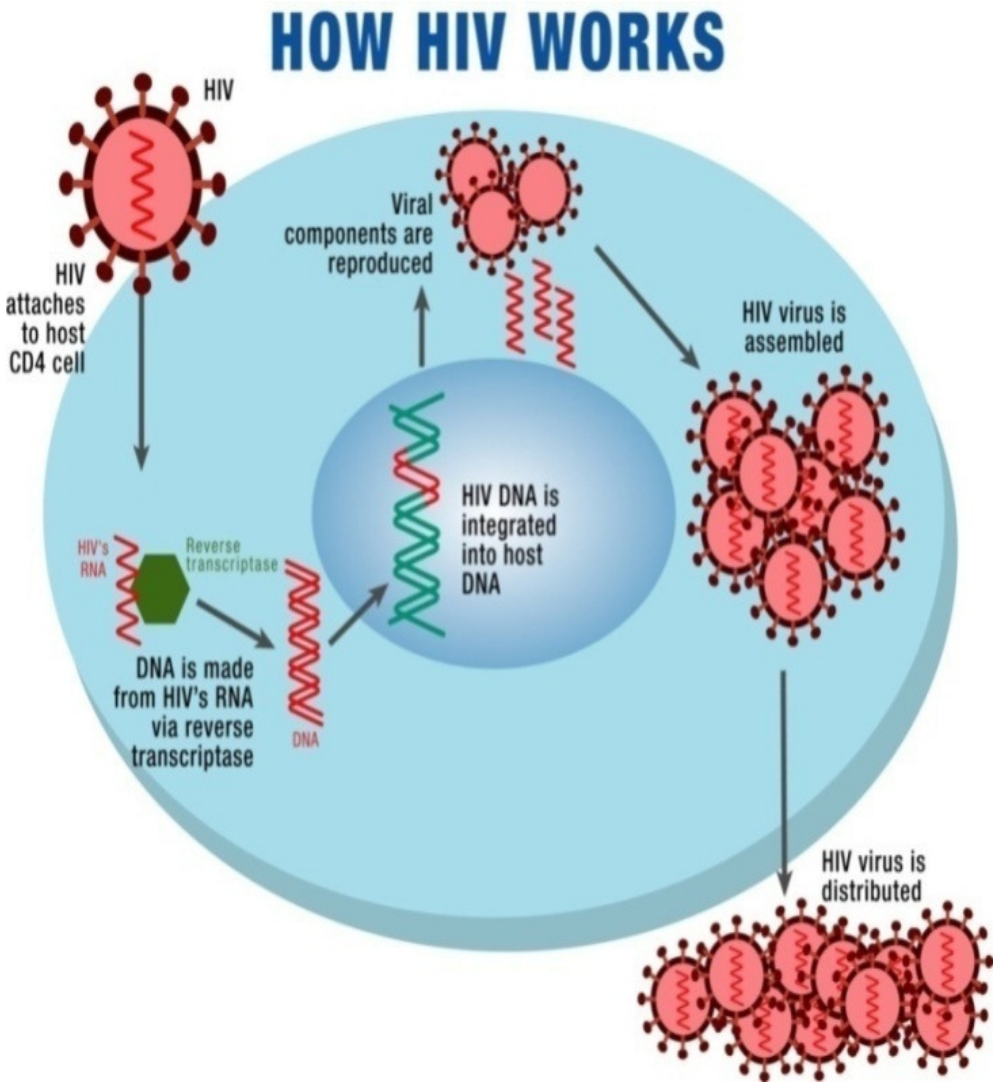
- 55KDA protein responsible for helper or inducer function of immune system.
- Also expressed on the surface of Monocytes /macrophages and Dendritic / Langerhan cells.

PATHOGENESIS

CELL TYPES INFECTED

- CD4 T cells
- Dendritic cells
- Monocytes/macrophages.
- Microglial cells
- Hofbauer cells

VIRAL REPLICATION IN CD4 CELL



PRIMARY HIV INFECTION

- Mucosal dendritic cells bind gp120 with DC-SIGN.
- Presents HIV to cells expressing CD4 molecule.
- Transported to regional Lymph node.
- Intense replication occurs in Lymph nodes.
- Reaches critical level and burst of viraemia occurs.
- Dissemination.
- Occurs 3-6 weeks after infection.
- Flu like illness – fever, arthralgia, rash lymphadenopathy.
- CD8 T Cells

CHRONIC & PERSISTENT INFECTION

Symptoms of acute viral disease disappear.

- Drop in the detectable free and cell associated virus in the blood.
- CD4 count almost normal level
- All virologic parameters in the peripheral blood are very low.
- Hallmark of HIV infection. Never eliminated completely.
- Trapped viruses in FDCs activate CD4 cells
- Lasts for 8-10 years in adult

ADVANCED HIV DISEASE

- Re emergence of free virus in both peripheral blood & lymph nodes.
- Decline in CD4 & loss of function.
- Emergence of faster replicating, more virulent strains.

- Loss of CD8 anti HIV activity.
- Disruption of lymphnode architecture and loss of dendritic cell network.
- Change of viral phenotype from NSI to SI.

Mechanism of CD4 depletion and dysfunction

- Direct damage by the virus.
- Immune mechanism triggered.
- Syncytium formation induced by virulent strains eliminates hundreds of uninfected cells.
- Nonvirologic mechanism – autoimmune, anergy, super antigens, apoptosis.
- Destruction of lymphocytes precursors.

0HIV IN CHILD DIFFERS FROM ADULT IN

- Developing more severe bacterial infection.
- Neuro-developmental problems.
- Rapid progression of disease.
- Higher mortality.
- Opportunistic Infection as a primary disease rather than reactivation.

PATTERN OF CLINICAL PROGRESSION

- Rapid progressors
- Slow progressors
- Long term survivors

RAPID PROGRESSORS

- Considered infected in utero
- Detectable virus within first 48 hours of life

- Symptomatic within first few months of life
- Median survival – 6-9 months
- Immuno competent cells will be infected before their migration to marrow, spleen, etc.
- Establishment of infection before immune system develops.

SLOW PROGRESSORS

- Considered infected intrapartum.
- Detectable after first week of life.
- Median survival - 6 years.
- Failure to thrive / Recurrent bacterial infection.
- Slow decline of viral load (due to immaturity of immune system)

LONG TERM SURVIVORS

- Considered infected during breast feeding.
- Manifest late in life (Considered as adult equivalents)
- Minimal or no progression of the disease.
- Relatively normal CD4 count and very low Viral load for longer than 8 years.
- Remain alive >20 yrs.

CLINICAL STAGING

- Suspect a case
- Define severity of disease
- Follow-up for disease progression
- Ascertain need to start ART
- Follow-up resonse to ART
- Prophylaxis for OI

IMMUNOLOGICAL STAGING

- Assessing immunodeficiency
- Early detection of worsening of disease
- Decision to initiate or switch ART

WHO CLINICAL STAGING

Primary HIV Infection

- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

  (enlarged lymphnode > 1cm at 2 or more non-contiguous sites)

Clinical Stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Recurrent oral ulcerations (2 or more in 6months)

- Unexplained persistent parotid enlargement.
- Linear gingival erythema
- Herpes zoster
- Recurrent or chronic respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) (>2episodes in 6months)

Clinical Stage 3

- Fungal nail infections
- Moderate unexplained malnutrition, not adequately responding to standard therapy (>2SD below weight-for-age)
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (>37.5 intermittent or constant, for longer than one month, with night sweats)
- TB lymphadenitis
- Pulmonary tuberculosis

- Persistent oral candida (outside first 6- 8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis/periodontitis
- Severe recurrent presumed bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis
- Chronic HIV-associated lung disease including bronchiectasis
- Unexplained anaemia (<8g/dl), neutropenia (<500/mm^3) or chronic thrombocytopenia (<50 000/ mm^3)

Clinical Stage 4

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy (>3SD below weight-for-age)
- Pneumocystis pneumonia
- Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

- Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Oesophageal candidiasis (or candida of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (outside the neonatal period)
- HIV-associated cardiomyopathy or HIV-associated nephropathy HIV encephalopathy.
- Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month.
- Extrapulmonary cryptococcosis including meningitis.
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
- Chronic Cryptosporidiosis

- Chronic Isosporiasis
- Disseminated non-tuberculous mycobacteria infection.
- Acquired HIV-associated rectal fistula.
- Cerebral or B cell non-Hodgkin lymphoma.
- Progressive multifocal leukoencephalopathy.

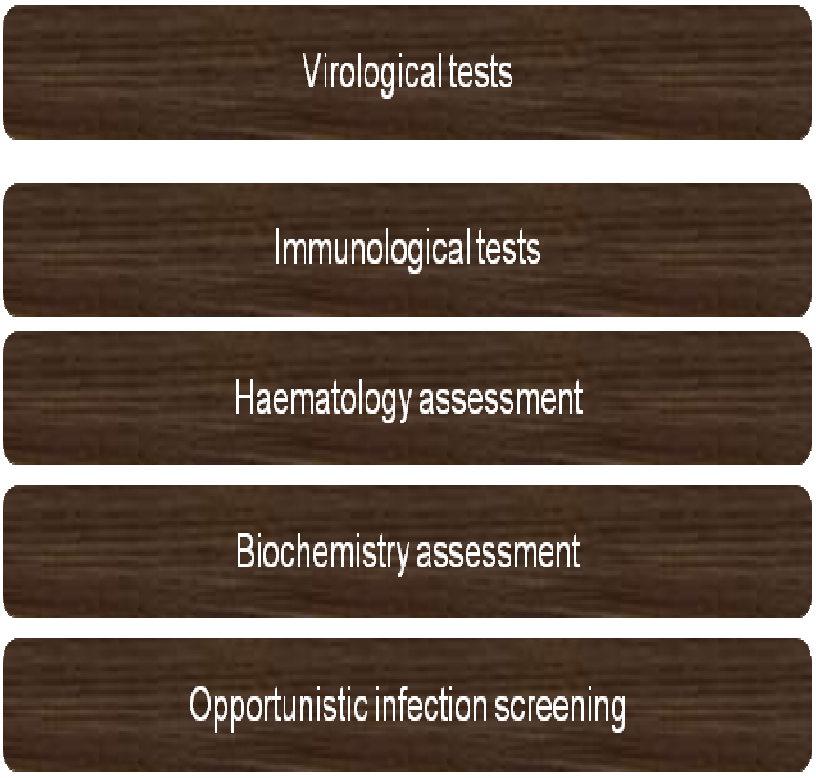
Clinical Signs Definitively - HIV Infection

- Some clinical conditions are very unusual without HIV infection
- Pneumocystis pneumonia
- Oesophageal candidiasis
- Lymphoid interstitial pneumonitis
- Kaposi's sarcoma
- Cryptococcal meningitis

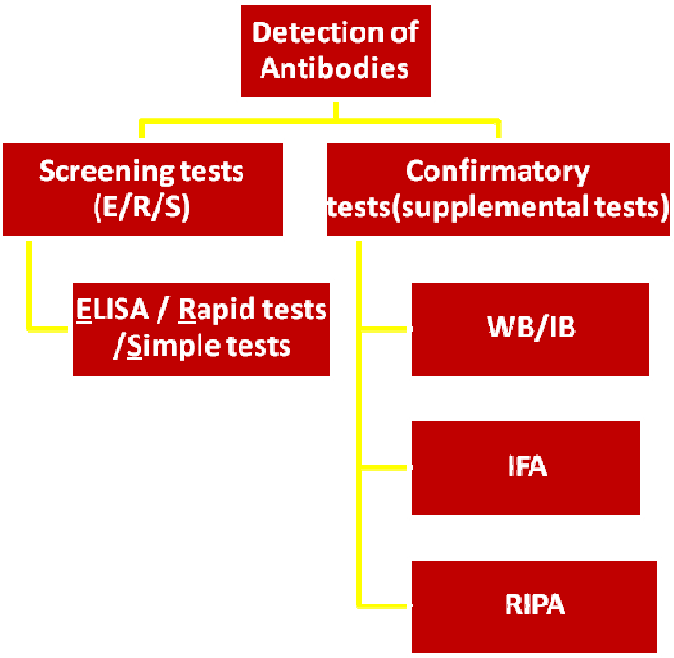
Diagnosis of these conditions thus suggests HIV infection

- Need to perform an HIV antibody test

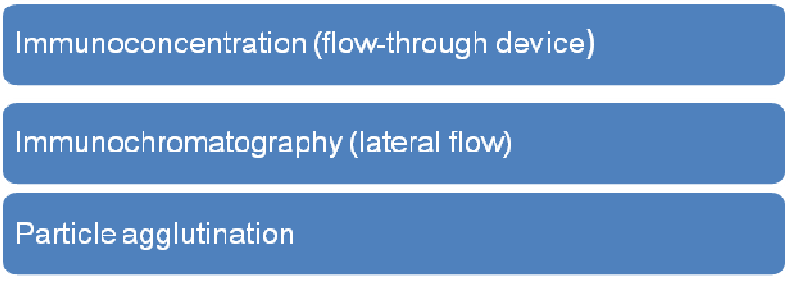
DIAGNOSIS



DIAGNOSTIC TESTS



Three Formats of HIV Rapid Tests



Advantages of Rapid Tests compared to ELISA

- More flexible (efficient for 1 to multiple tests at a time)
- Does not required highly trained or skilled staff
- On-site clinic testing can be performed easily
- Very easy to interpret test results (naked eye)
- Samples can obtained less invasively (finger-prick) - safer to lab technician
- ***Same-day screening and*** *confirmation of results (available <30 min.) as compared to ELISA (3hours)*

IMMUNOLOGICAL STAGING

Classification of HIV associated immunodeficiency	Age-related CD4 cell values			
	< 11 months (%)	12-35 months (%)	36-59 months (%)	>5 years (cells/cu.mm)
Not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
advanced	25-30	20-25	15-20	200-349
Severe	<25% or <1500cells	<20% or <750cells	<15% or <350cells	<15% or <200 cells/cu.mm

WHO GUIDELINES (REVISED) 2010 FOR ART INITIATION IN INFANTS AND CHILDREN

<table>
<tr><th rowspan="2">WHO Paediatric Stage</th><th rowspan="2">Availability of CD4 cell measurement</th><th colspan="4">Age-specific treatment recommendation</th></tr>
<tr><th><12months</th><th>13-24months</th><th>2-5yrs</th><th>>=5yrs</th></tr>
<tr><td rowspan="2">3 & 4</td><td>CD4</td><td colspan="4" rowspan="2">Treat all</td></tr>
<tr><td>No CD4</td></tr>
<tr><td rowspan="2">1 & 2</td><td>CD4</td><td colspan="2" rowspan="2">Treat All</td><td>Absolute CD4<=750cells/mm3 or %CD4 < 25%</td><td><=350 cells/mm 3</td></tr>
<tr><td>No CD4</td><td colspan="2">Don't treat</td></tr>
</table>

ANTIRETROVIRAL PROPHYLAXIS: MONOTHERAPY

- **Nevirapine (NACO Guidelines)**
    - Mother – Single dose NVP 200mg onset of labour.
    - Baby - Syrup NVP 2mg/kg within 72 hours of delivery.
- **AZT (Not as per NACO Guidelines)**
    - Mother
        - AZT from 14 weeks, Intrapartum (PACTG 076)
        - AZT from 28 weeks, Intrapartum (PHPT 1 Thai Long)
        - AZT from 36 weeks, Intrapartum (PHPT 1 Thai Short)
    - Baby - Syrup AZT 2mg/kg qid for 6 weeks
    - Antiretroviral Therapy
- Indicated for maternal health at clinical stage 3 & 4

- Mother
    - CD4 < 200 =AZT + 3TC + NVP (start any time)
    - CD4 250 to 350 = AZT + 3TC + EFV (after first trimester)
- Baby
    - Syrup AZT 2mg/kg qid for 4 weeks

ANTI RETROVIRAL THERAPIES:

Nucleoside/ Nucleotide transcriptase inhibitors (NRTIS)

DRUGS	**DOSAGE**
Abacavir	children >3 months to 18yrs:
Ziagen, ABC 300 mg	8mg/kg PO bid
Oral solution 20mg/ml	
Didanosine	120 mg/m^2 PO bid
(Chewable buffered tablets,	
Buffered Powder packets)	

Emtricitabine	200 mg capsule PO once daily
Emtriva, FTC capsules	
Stavudine	1 mg/kg PO bid
Zent, d4T	

Non- Nucleoside/ Nucleotide transcriptase inhibitors (NNRTIS)

DRUGS	DOSAGE
Efavirenz	
Sustiva,EFV	Get once daily PO at bed time
	Weight 10-15 kg 200mg
	15- 20kg 250mg
	20 - 25kg 300mg
Nevirapine	<8 yrs - 4mg/kg PO once daily for 14 days
Viramune, NVP	>8 yrs- 4mg/kg PO bid, if tolerated
Tablet 200mg	
Suspension : 10mg/ml	

PROTEASE INHIBITORS

Amprenavir	4-16yrs and weighing <50kg
Agenerase,APV	oral solution 22.5 mg/kg bid >50kg
Liquid formulation :15mg/ml	1400mg/dose PO bid(max 2800mg/dose)
Capsules: 50mg	
Atazanvir	not established
Reyataz ATV	
Darunavir	limited data on paediatric dosing
Lpinavir/ Ritonavir (co-formulated)	7-<15kg: 12mg LPV & 3mg RTV/kgPO
Ritonavir	200mg/m fo every 12hrs
Saquinvir	not established
Tipranvir	limited data on safety

FUSION INHIBITORS

Enfuvirtide >6yrs 2mg/kg bid

The Four Prong Model for Prevention of Mother to Child HIV Transmission: NACO

Prong 1

- Primary Prevention of HIV Infection Among Women of Child Bearing Age and Young People.

Prong II

- Prevention of Unintended Pregnancy Among HIV Infected Women

Prong III

- Prevention of HIV Transmission from infected mother to her infant.

Prong IV

- PPTCT Plus Provide Care and Support for HIV-infected Women and their Families

PPTCT FLOW CHART

Positive mothers

↓

Counseled for MTP / mode of delivery / Infant feeding / STI / TB / Risk reduction Strategies

↓

Nevirapine prophylaxis to mother during labour

↓

Neonate Monitoring

↓

Nevirapine to the new born (within 72 hrs)

↓

Follow up (PNC OPD, well baby clinic)

↓

HIV testing Baby 18 months

↓

Continuum, Care and Support (ART / OIs, Diet / nutrition, referrals NGO / CBOs)

IMMUNISATION

Recommendations for these vaccines differ from those for Immuno-competent children:

- BCG
- Polio vaccine
- Measles/MMR
- Rotavirus vaccine
- Varicella vaccine

- **MEASLES** - The WHO recommends measles vaccine at 6 months of age, followed by a second dose at 9 months of age.

- **MMR** - The first dose at 1 Year of age. Second dose 1 month after the first dose rather waiting until age 4 to 6 years.

- **PNEUMOCOCCAL VACCINE** - Children <2 Yrs should be vaccinated according to the routine PCV schedule.

- For incompletely vaccinated children aged 2-5 Yrs:

1. administer two doses of PCV at least 8 weeks apart.

2. should also receive the 23-valent pneumococcal polysaccharide vaccine (PPV) ≥2 months after their last PCV dose with a single revaccination with the 23- valent vaccine 3–5 years later

REVIEW OF LITERATURE

1. Sandeep B. Bavdekar, etal

- This was a prospective study conducted between children age 18 month and above admitted here tertiary care center in Mumbai, India, with a given clinical features

- They were subjected to HIV testing using WHO UNAID strategy II

- The Data obtained was analyzed using SPSS software programs.

RESULTS

- 23 of the 115 (20%) children tested positive for HIV.
- Sero positivity - 83.3% - chronic dermatitis
  - 9.1% - chronic diarrhea
- Oral thrush, generalized dermatitis and generalized lymphadenopathy were the other significant factors predicting HIV seropositivity.
- The probability of HIV infection was higher in children who had higher number of risk factors present concomitantly.

CONCLUSION:

The probability of HIV infection in a child is dependent upon the nature and number of manifestation present.

2. Karande, etal -

- This was a prospective study conducted children age group between 1 month to 12 years admitted at the department of paediatrics and microbiology LTMG Hospital Mumbai, India, with the given clinical features tested with ELISA.

RESULTS

- 24 Of the 204 children (110 male, 94 female) screened, were diagnosed as HIV infected.

- Seropositivity:

40.6%	- oral candiasis.
18.2%	- chronic diarrhea
16.2%	- disseminated Tuberculosis
14.4%	- severe malnutrition
11.2%	- serious pyogenic infections

- Increase in number of risk factors increases the chance of the patient being HIV infected.

CONCLUSION: Clinically directed screening does have a practical role in diagnosing HIV infection in a poor resource setting.

3.Pol RR, etal

This study was conducted in proven HIV sero positive children aged between 1 1/2years to 12 years who are admitted between Apr 2004 – June 2005 to pediatric ward KIMS ,Kubli with a given clinical features.

RESULTS :

- No of HIV sero positive patients admitted during the period of was 71
- The major route of transmission was vertical transmission with a percentage of 94.37%

Common Symptom:	**Common opportunistic infections**	
➢ Persistent Fever -70.42%	Tuberculosis	-38.03%
➢ Persistent cough – 59.15%	Recurrent Diarrhoea	-30.99%
➢ Loss of appetite – 59.15%	Oral Candidiasis	-21.13%
➢ Lymphadenopathy –57.75%	Recurrent Bacterial	
➢ Severe malnutrition -54.95%	Pneumonia	-12.68%

- Six children died during study period – 8.45%
- which includes 4 cases of HIV – encephalopathy -5.63%

CONCLUSION:

The major route of HIV infection was vertical transmission . Persistent fever, cough, loss of appetite and weight loss were common presenting clinical features. Tuberculosis was the commonest opportunistic infection.

4.**Shah. SR, etal –**

- This prospective study was conducted from Jan 2000 - Oct 2001 at Mumbai's territory care & referral teaching hospital, India.

- Children aged between 1 month to 12 years were admitted and tested for HIV +ive by triple ELISA test, were enrolled in the study .

- Status of children more than 18 months of age was confirmed by DNA –PCR testing for HIV.

RESULTS :

- 50 positive children enrolled (31 male 19 female)

- 42 were perinatally infected ,

- 8 were infected via blood transfusion.

Clinical Features

- PEM -90%
- Fever for morethan 1 mth -50%
- Weight loss for more than1 mth -50%
- Persistent generalized
- Lymphadenopathy – 24%
- Skin manifestations – 79 %
- Patients died - 6 (mortality 14 %).

Opportunistic infections noted

Tuberculosis -19 cases

Candidiasis – 6 cases

Pneumocystis Carinii

Pneumonia – 4 cases

Herpes zoster – 3 cases

Giardiasis - 1 case

CONCLUSION:

The most common mode of acquiring HIV is perinatal transmission in the pediatric age group. Most of the children who were tested +ive have protein-energy malnutrition. The most common in HIV-infected Indian children was Tuberculosis. Patients with HIV-encephalopathy have less outcome.

5.Merchant RH et al –

- This prospective study was conducted between July 1994- 1996 in Wadia Children hospital at Mumbai

- 100 patients were enrolled out of that 50 children with disseminated TB and 50 with chronic diarrhea were tested for HIV sero positivity.

- All the children in the study were subjected to Elisa testing using the NOVOPATH HIV1 and 11 EIA kit of Bio rad Labs.

- The child was declared HIV seropositive only after confirming the test taken by using the 2 different Elisa methods for sero positive.

Disseminated TB - 9 children with a percentage of 18% and for

Chronic diarrhea -12 children with a percentage of 24% were tested HIV seropositive , taking the total seropositivity to 21%.

The commonest mode of transmission 71% was pereinatal. The children with chronic diarrhea 40% had associated oral candiasis and some others 10% had both oral perianal candiasis. Out of the 21 children who were HIV positive 6 children expired during the study period of 2 years with extensive Tubercluosis (3)and chronic diarrhea(3).

6.**Mukadi et al –**

This was study of case-control and prospective nature. The study period for this study was done during the month of March 1994 and November 1995. Children of age group from 0 till the age of 9 years were considered. The study was done in diagnosed two TB centers and 2 principal university hospitals in Abidjan, Cote d'Ivoire. Children were diagnosed serum samples were collected for HIV tests and lymphocyte phenotyping. X-ray of the chest was taken. Acid-fast bacilli smear and culture tests were done by taking the gastric aspirates and sputum samples. Then followup were done for the children every 2 months during a course of standard 6-months anti-TB therapy. To examine risk factors for TB, the siblings of children referred for TB skin testing on the basis of age and sex matched healthy control children.

Results:

- During this study a total of 161 children who have TB were enrolled which includes 39 children with pulmonary TB which was culture confirmed that accounted to 24% , 80 children had clinically diagnosed pulmonary TB, that

accounted to 50%, and with extrapulmonary TB was 42 children which accounted to 26%. Children with TB were significantly more likely than 161 control children to be HIV +ive (19 versus 0%), to have a past history of TB (55 versus 16%) and to live in below poverty line status housing (24 versus 6%).

- No prominent differences between HIV-sero+ive and sero-ive children were found in the distribution of radiologic abnormalities for pulmonary TB or in the site of extrapulmonary TB.

- The rate of mortality in children with HIV+ive was significantly more than in children with HIV-ive and with available lymphocyte subtyping results all deaths in HIV-seropositive children occurred in those percentage of <10% CD4.

Conclusions: This study implies the HIV infection is the important significant risk factor in the development of Tubercluosis in children. The mortality rate in this area due to HIV related immunosuppression is the major critical risk factor in this population.

7.Chan, Siu Pun et al -

Atypical clinical manifestations and rapid progression of tuberculosis disease (TB) are well-recognized in adults with the acquired immunodeficiency syndrome (AIDS). There are few reports of children with AIDS and TB. We report the manifestations, clinical course and outcome of 12 pediatric patients with AIDS and TB.

The charts of all children admitted to our institution, from 1989 through 1994, with the diagnoses of AIDS and culture-proved TB were reviewed.

***Results*:** Twelve children between the ages of 2 months and 13 years fit the criteria. The mean time between the diagnosis of AIDS and TB was 20 months. The most frequent presenting symptoms were fever (75%) and tachypnea (33%). All had negative Mantoux tests (5 tuberculin units of purified protein derivative). Extrapulmonary TB was present in 3 (25%). A source case was identified for 4 (33%). Previous pulmonary disease was present in 7 (58%). Chest roentgenograms were abnormal in 11 (91%), with diffuse interstitial infiltration the most common finding. Susceptibility tests were performed on 10 strains, 3 of which were resistant to 1 or more antituberculosis drugs. Three patients (25%) died of TB, 1 of whom was appropriately treated with antituberculosis drugs but had a strain resistant to isoniazid and rifampin.

***Conclusion*:** Children with AIDS and TB most frequently present with atypical manifestations of TB. A high index of suspicion is needed to correctly diagnose TB in this group of children. Early diagnosis is important because most respond well when treated appropriately.

STUDY JUSTIFICATION

- HIV infection present with several manifestations none of them is specific; hence several children are subjected to HIV testing.

- Few studies carried out to determine the likelihood of HIV infection with a given clinical features in Indian children.

- If we know exactly the symptom / sign which are most predictive of HIV infection, we would be able to screen these children for the evidence optimally with out any over / under estimation.

- Ours being one of the premier institute in south east Asia catering the health care of children, the study could be helpful in providing clinical features for early diagnosis /reference /and follow-up.

AIM OF THE STUDY

To determine the probability of HIV infection when a child is presenting with,

a) One of the selected clinical features and

b) in combinations.

SUBJECTS AND METHODS

1. METHODOLOGY

STUDY DESIGN

Descriptive study

STUDY PLACE

In patients and out patients department, ICH.

STUDY PERIOD

Jun 2011 to oct 2012.

STUDY POPULATION

Cases with the given clinical features attended in out patient department and admitted in Inpatient department of ICH and HC, Egmore, Chennai.

CASE DEFINITION

Recurrent Pneumonia

Cough with tacypnea, (respiratory rate 50 or more in children aged 1yr to 5yrs and 25 or more in 6 to 12yrs with radiological clearance in between 2 episodes of pneumonia).

Persistent diarrhea

2 or 3 loose stools per day for more than 14 days

Ear Discharge

Ear pain or ear discharge from patient history or visible pus draining from ear or tender swelling behind ear. If reported less than 14 days is acute and if more than 14days, its chronic.

Very low weight or Severe malnutrition

Grade II, III & IV malnutrition (as per weight for age)

Oral thrush

White patches in mouth which can be scraped off or red patches on tongue, palate, or lining of mouth, usually painful or tender.

Parotid enlargement

Asymptomatic bilateral parotid swelling of unknown cause, usually painless.

Generalized Lympadenopathy

Enlarged lymph nodes more than 1cm at 2 or more non contiguous sites of unknown cause.

Chronic or refractory skin or mouth conditions

If chronic (lasting for more than 3 months) or a re refactory (do not respond to standard therapy), they include: Papular itching rash, ring worm, scabies, impetigo, seborrhea, gum and mouth ulcers.

Disseminated TB

Millary, CNS, Pulmonary Tuberculosis

Hepatomegaly

Enlarged liver (liver span more than that of normal for that age)(no obvious cause).

Encephalopathy

Generalized disorder of cerebral function (no obvious cause)

Fever for more than one month

unexplained fever for more than one month.

Inclusion criteria

Children between the age group of 18 months to 12 years who met the case definition for HIV.

Sample size: All suspected children with the age group between 18 months to 12 years were enrolled.

MANOEUVRE

- All children satisfied the inclusion criteria during the period of study was recruited.
- Demographic data, history and examination findings and test results were recorded in a pre designed proforma.
- Blood sample from suspected cases will be collected and sent to ICTC, ICH for screening of HIV.

- Test for HIV : Rapid screening test -

  (i) Immunodot assay

  (ii) Immuno Chromato graphic based assay

  (iii)Immuno Concentration based assay

1. STATISTICAL ANALYSIS:

The proportion of various clinical features among seropositive and seronegative for HIV were compared using chi-square test. The association of clinical features to seropositivity was measured also by multivariant analysis of arriving at Odds Ratio with 95% confidence interval OR (95% CI) and adjustable OR (95% CI). $P<0.05$ was consider for statistical significance. The trend of association between number of clinical features with proportion of seropositivity was analysed with chi-square test for trend.

2. ETHICS

Patient consent and IRB approval obtained.

OBSERVATIONS

Total cases screened : 1647

Number of cases with HIV positivity : 24

Totally 1647 children were screened, from June 2011 to October 2012 with the age group between 18 months and 12 years were enrolled in this study. Out of whom 991 (60%) children were males and 656 (40%) were females.

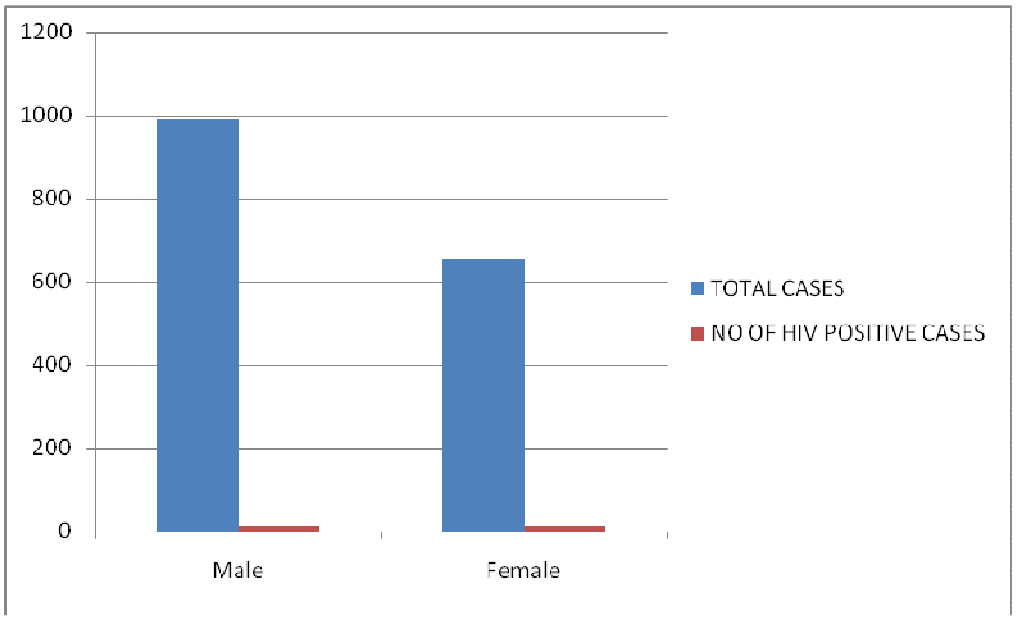


Fig.1.Comparison of sex distribution among HIV positive and negative children

Among these 1647 children, 24 were HIV positive out of whom 11 (46%) children were male and 13 (54%) children were female with male to female.

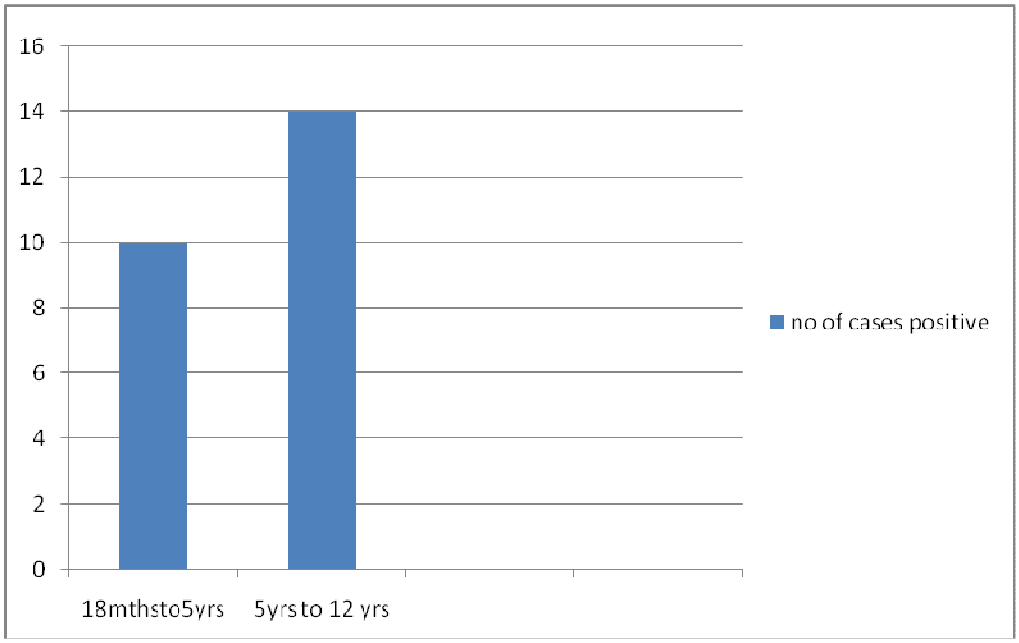


Fig. 2.Comparision of age distribution of HIV positive cases

Among the 24 HIV positive children, 10 (42%) children were between the age group 18 months to 5yrs and 14 (58%) children were between the group 5yrs to 12 yrs.

Occupational status of parents of HIV positive children

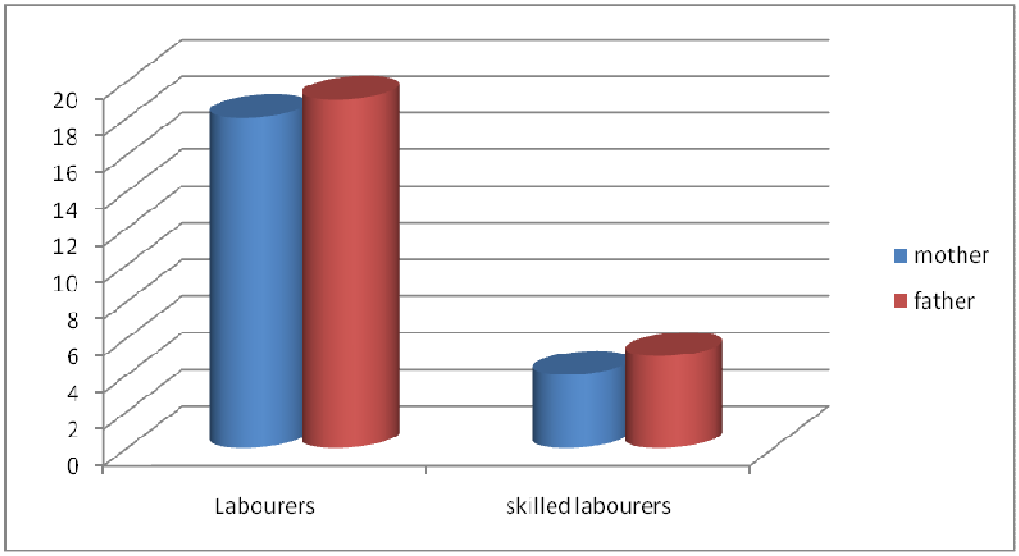


Fig.3.Occupational status of parents of HIV positive children

Among 24 HIV positive children the occupational status of their parents was analysed. Most of the mothers, that is 18(75%)of them were labourers and 6(25%) were skilled labourers. Same was in the case of fathers, 19(79%)were labourers and 5(21%) were skilled labourers.

Table - 1

Clinical Features in relation to Serological Status for HIV Infection

Clinical Manifestations	HIV sero (+ive)	HIV sero (-ive)	P-Value
Recurrent Pneumonia	4 (16.7%)	43 (2.6%)	0.004
Persistent diarrhea	3 (12.5%)	21 (1.3%)	0.005
Chronic Ear discharge	1 (4.2%)	2 (0.1%)	0.043
Very low weight or severe malnutrition	3 (12.5%)	15 (0.9%)	0.002
Oral thrush	0 (0.0%)	11 (1.5%)	0.850
Bilateral Parotid enlargement	0 (0.0%)	2 (0.1%)	0.971
Generalized lymphadenopathy	1 (4.2%)	15 (0.9%)	0.210
Chronic or refractory skin or mouth conditions	2 (8.3%)	15 (0.9%)	0.024
Disseminated TB	2 (8.3%)	9 (0.6%)	0.010
Hepatomegaly (No obvious cause)	1 (4.2%)	5 (0.3%)	0.084
Encephalopathy(No obvious cause)	1 (4.2%)	6 (0.4%)	0.098
Fever more than 1 month	6 (25.0%)	77 (4.7%)	0.001

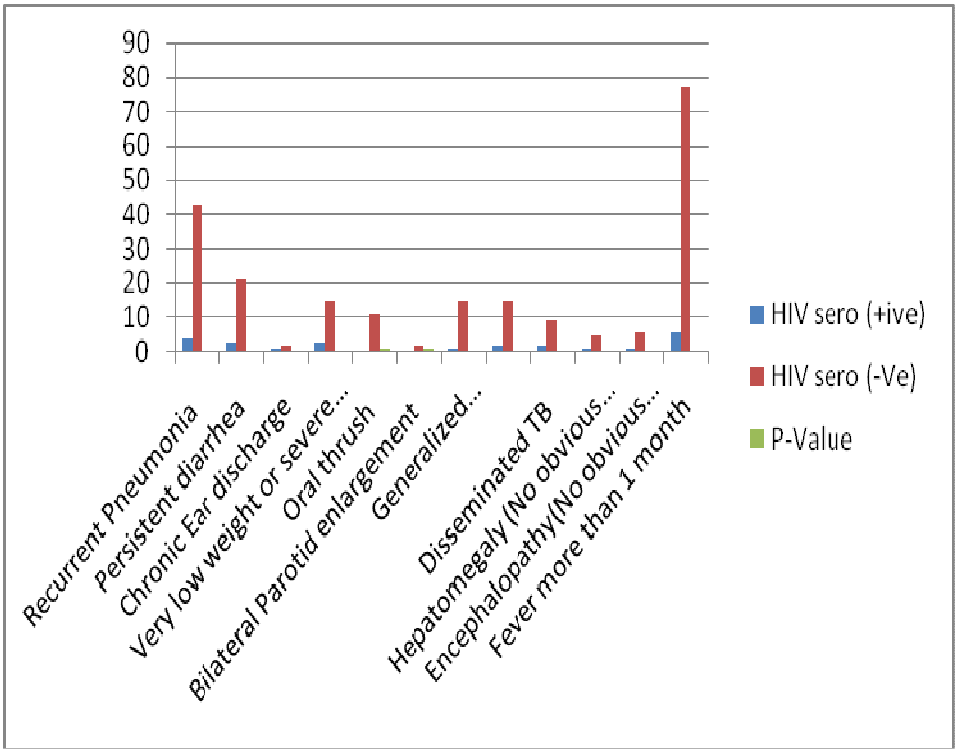


Fig.4.Comparison of Sero positivity and Negativity of HIV Positive children

Table - 2

Clinical features in relation to Univariate analysis

Clinical manifestations	Odds Ratio	95% C.I.
Recurrent Pneumonia	7.35	2.41 – 22.42
Persistent diarrhea	10.90	3.02 – 39.35
Chronic Ear discharge	35.24	3.08 – 402.5
Very low weight or severe malnutrition	15.31	4.12 – 56.88
Oral thrush	-	-
Bilateral parotid enlargement	-	-
Generalized Lymphadenopathy	4.66	0.59 – 36.78
Chronic or refractory skin or mouth conditions	9.74	2.10 – 45.20
Disseminated TB	16.30	3.33 – 79.9
Hepatomegaly (No obvious cause)	14.07	1.58 – 125.2
Encephalopathy (No obvious cause)	11.72	1.36 – 101.3
Fever for more than one month	6.69	2.58 – 17.34

Recurrent pneumonia was observed among 4 cases out of 24 cases who were serologically positive for HIV when compared to 43 (2.6%) among 1623 sero negatives (P:0.004), Odds of having Recurrent Pneumonia was 7 times more among seropositives when compared to seronegatives [OR with 95% CI = 7.(35 2.41 – 22.42)].

Three children (12.5%) among HIV positives had persistant diarrhea when compared to 1.3% among who were tested negative for HIV serology. Possibility of a child with chronic diarrhea among HIV positives is 10 times more likely when compared to those who were seronegatives. [OR with 95% CI = 10.9 (3.02 – 39.35)].

One child (4.2%) among HIV positives had chronic ear discharge when compared to 0.1% among who were tested negative for HIV serology. Possibility of child having chronic ear discharge among HIV positive is 35 times more likely when compared to those who were seronegative [OR with 95% CI = 35.24 (3.08 – 402.5)].

Three children (12.5%) among HIV positives had very low weight when compared to 0.9% among who were tested negative for HIV serology. Possibility of child having very low weight among HIV positive to 15.31 times more likely when compared to those who were seronegative.[OR with 95% CI = 15.31 (4.12 – 56.88)].

11 (1.5%) children with oral thrush were negative for HIV serology. No children with oral thrush found to be HIV positive. P-value was 0.850.

Two (0.1%) children with Bilateral parotid enlargement were negative for HIV serology. No children with Bilateral parotid enlargement found to be HIV positive P-value was 0.971.

One child (4.2%) among HIV positives had generalized lymph adenopathy when compared to 15 (0.9%) who were tested negative for HIV serology. Possibility of a child having generalized lymph adenopathy among HIV positives is 4 times more likely when compared to those who are seronegatives [OR with 95% CI = 4.66 (0.59 – 36.78)].

Two children (8.3%) among HIV positives had chronic refractory skin infection when compared to 15 (0.9%) among who were tested negative for HIV serology. Possibility of a child having Chronic refractory skin infection among HIV positives is 9 times more likely when compared to those who were seronegatives [OR with 95% CI = 9.74 (2.10 – 45.20)].

Two children (8.3%) among HIV positives had disseminated TB when compared to 9 (0.9%) among who were tested negative for HIV serology. Possibility of a child having disseminated TB among HIV positives is 16 times more likely when compared to those who were seronagatives [OR with 95% CI = 16.30 (3.33 – 79.97)].

One child (4.2%) among HIV positive had hepatomegaly (no obvious cause) when compared to 5 (0.3%) among who were tested negatives for HIV serology. Possibility of a children having hepatomegaly (no obvious cause) among HIV positive was 14 times more likely when compared to those who were seronegatives OR with 95% CI = [14.07 (1.58 – 125.2)]

One child (4.2%) among HIV positives had encephalopathy (no obvious cause). When compared to 6 (0.4%) among who were tested negative for HIV serology. Possibility of a child having encephalopathy (no obvious cause) among HIV positives is 11.72 times more likely when compared to those who are seronegative [OR with 95% CI = 11.72 (1.36 – 101.3)].

Six children (25.0%) among HIV positives had fever more than one month when compared to 77 (25.0%) among who were tested negative for HIV serology. Possibility of a children with fever more than one month among HIV positives is 6.69 times more likely when compared to those who are seronegative [OR with 95% CI = 6.69 (2.58 – 17.34)].

Table - 3

HIV seropositivity in relation to the number of clinical features present

No. of clinical features	HIV positive cases	HIV negative cases	P-value
1	4 (5.0%)	76 (95.0%)	0.003
2	10 (9.1%)	100 (90.9%)	
3	6 (13.3%)	39 (86.7%)	
4	4 (40.0%)	6 (60.0%)	

When there was a single clinical features predicting HIV positivity was 5% when compare to 40% among those who had 4 clinical features. There was steady increasing trend of seropositivity from one feature to four features which was found to be statistically significant (P = 0.003).

DISCUSSION

Human immunodeficiency virus(HIV) is estimated to be constituted by 3 to 5% by paediatric age group less than 15 years amondg all cass reported. The registered paediatric cases at various institutions are far below the estimated.

38.6 million - HIV infection world over, 2.3 million, i.e. 5.9 % - children <15 years of age. In 2007- 5,40,000 children were born with HIV infection transmitted from their infected mothers. 90% - sub-saharan Africa & remaining in Asia , mainly in India Estimated total no. of HIV infection in India 3.97 million – 2001,5.1 million – 2003, 5.134 million – 2004, 6.13 million – 2010, No. Of children living with HIV in India – 0.17 million (UNAIDS report 2004) to 0.24 million (NACO estimate).

In India, it is divided into 3 zones. High prevalence - HIV prevalence in ANC mothers > 1%. Medium prevalence - < 1% but in high risk population in STI clinics >20%. Low prevalence - <1% & in high risk < 20% High prevalence – (6) Maharashtra, Karnataka, Tamilnadu, Andhrapradesh, Manipur, Nagaland. Medium prevalence – (2) Gujarat, West Bengal Low prevalence – rest of states. National average of HIV prevalence in AN mothers – 0.7% MTCT- 15 to 30%- non-breastfeeding population, 30 to 45% - breastfeeding population.

We suspect HIV infection when a child presents with the given clinical feature either in single or combined like recurrent pneumonia, persistent diarrhea, ear discharge, very low weight or severe malnutrition, oral thrush, parotid enlargement, generalized lympadenopathy, chronic refractory or mouth conditions, disseminated TB, hepatomegaly, encephalopathy, fever for more than one month.

There is a possibility of other conditions with these symptoms or signs, with this background review of literature was done.

In our study we found 24 children were diagnosed as HIV infection positive. Out of them in our study, seropositivity for recurrent pneumonia (16.7%), persistent diarrhea(12.5%), ear discharge (4.2%), oral thrush(0%), very low weight or severe malnutrition(13.6%), parotid enlargement(0%), generalized lympadenopathy(4.2%), chronic refractory or mouth conditions(8.3%), disseminated TB(8.3%), hepatomegaly(4.2%), encephalopathy(4.2%), fever for more than one month(25%).

Karande, etal conducted study between 1 year to 12 years admitted at the department of pediatrics and microbiology LTMG Hospital Mumbai. Out of 204 children screened 24 were diagnosed as HIV infected. The sero positivity was 40.6% for oral candiasis, 18.2% for chronic diarrhea, 16.2%for disseminated TB, 14.4% for severe malnutrition, 11.2% for serious pyogenic infections. This study concluded that clinically directed screening does have a practical role in diagnosing HIV infection in a poor resource setting. The diagnostic test was done by Elisa.

In our study, we included the age group between 18 months and 12 years of age, out of 1647 children screened 24 were diagnosed as HIV infected. In our study the seropositivity of clinical features compared to Karande, et al study were for recurrent pneumonia (16.3%), persistent diarrhea(12.5%), ear discharge (4.2%), oral thrush(0%), very low weight or severe malnutrition(12.5%), parotid enlargement(0%), generalized lympadenopathy(4.2%), chronic refractory or mouth conditions(8.3%), disseminated TB(8.3%), hepatomegaly(4.2%), encephalopathy(4.2%), fever for more than one month(25%). The diagnostic test was done by rapid screening test no children with oral thrush was found to be seropositive compared to Karande, etal study.

Pol RR, etal study was conducted in proven HIV sero positive children aged between 18 months to 12 years admitted between Apr 2004 to June 2005 in pediatric medical ward KIMS, Kubli with the given clinical features. The seropositivity for persistent fever was 70.42%, persistent cough 59.15%, loss of appetite 59.15%, lymphadenopathy 57.75%, severe malnutrition 54.95%, tuberculosis 38.03%, recurrent diarrhea 30.99%, oral candidiasis 21.13%, recurrent bacterial pneumonia 12.68%. Six children died during study period 8.45% which includes 4 cases of encephalopathy 5.63%. Vertical transmission was the major route of HIV infection. Persistent fever, cough, loss of appetite and loss of weight were common presenting clinical features. Tuberculosis was the commonest opportunistic infection.

In our study seropositive for fever more than one month was 25.0% when compared to Pol RR, etal study it was 70.42%. In our study the following clinical features emerged a independent predictors of HIV infection were fever more than one month, Very low weight or severe malnutrition, Recurrent pneumonia, Persistent diarrhea which were compared similar to Pol RR, etal study.

Merchant RH etal- In his study 18% seropositive for Disseminated TB and 24% for chronic diarrhea. In our study Disseminated TB 8.3% and 12.5% for chronic diarrhea. In his study children were subjected to Elisa, in our study children were subjected to Rapid screening test.

Sandeep B. Bavdekar, etal- In his study 83.3% seropositive for chronic dermatitis compared to our study was 8.3%. In his study showed oral thrush was significant risk factor compare to our study we did not find that oral thrush was as a significant clinical feature for HIV sero status.

In our study severe malnutrition was 12.5% compared to 90% PEM in Shah. SR, etal- study and also found that skin manifestations of his study were 79% compared to our study was 8.3%.

Recurrent Bacterial Pneumonia was 16.7% sero positive and Generalized lymphadenopathy was 4.2% in our study compared to Pol RR, etal- study Recurrent Bacterial Pneumonia was 12.68% sero positive and Generalized lymphadenopathy was 57.75%.

CONCLUSION

- Clinical profile of HIV in our study correlates with other literature.

- In our study, the following clinical features emerged a independent predictors of HIV infection.

    1. Fever more than one month
    2. Very low weight or severe malnutrition
    3. Recurrent pneumonia
    4. Persistent diarrhea

- Other important clinical features were chronic Ear discharge, disseminated TB, Hepatomegaly, recurrent skin infections.

- There was an increasing trend in rate of sero positivity with single to more number of these clinical features.

LIMITATION

Our study has its share of limitations also as we did not included children below 18 months as diagnosing HIV infection in them would have entailed performance of HIV DNA PCR. This was not possible due to financial constraints.

RECOMMENDATION

- If a child presenting with the above clinical features in single or in combination should be suspected to have HIV infection and investigated accordingly. This will avoid ordering HIV Testing in un warranted situations.

- From this if we know exactly the symptoms / signs which are most predictive of HIV infection, we would be able to screen these children for the evidence optimally with out any over / under estimation.

A DISSERTATION ON

CLINICAL FEATURES DIRECTED SCREENING FOR HIV INFECTION AMONG CHILDREN ATTENDING AN URBAN REFERRAL CENTRE

M.D (BRANCH VII)

PAEDIATRIC MEDICINE

THE TAMIL NADU
DR.MGR. MEDICAL UNIVERSITY.

APRIL 2013

INSTITUTE OF CHILD HEALTH AND HOSPITAL
FOR CHILDREN,
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